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Abstract: Atherosclerosis has become widely accepted as a chronic inflammatory disorder. Inflammation has been the key ingredient in the progression of atherosclerosis. C-reactive protein is an effective bio-marker for inflammation and has been shown to be a better predictor of the risk of atherosclerotic events than low-density lipids. Testing for CRP will provide another valuable tool for nurse practitioners to identify patients at risk for future events.

According to the American Heart Association (AHA) the cost of cardiovascular diseases and stroke in the United States in 2003 is estimated at $351.8 billion. Cardiovascular diseases remain the leading cause of morbidity and mortality in this country. AHA estimates that this year 650,000 Americans will have a new coronary attack and about 450,000 will have a recurrent attack related to artherosclerosis.[1] Primary prevention has included identifying the risk factors for an artherosclerotic event through taking a careful history, obtaining cholesterol levels, modifying lifestyle, and if needed prescribing pharmacological intervention.

The role of inflammation in the progression of atherosclerosis is becoming better understood.[2,3,4] The inflammatory marker C-reactive protein (CRP) can indicate low-grade chronic inflammation, which can identify patients at risk for athrosclerotic complications.[3] CRP can add to prognostic information that is provided by the traditional methods of identifying risk factors. This article reviews the inflammation process of artherosclerosis, defines CRP, and describes how CRP can be used as a tool for primary prevention.

Atherosclerosis-An Inflammatory Process

Atherosclerosis is an inflammatory disease.[2,3,4] The signs of inflammation in the artery wall occur concurrently with increased lipid accumulation.[3] The response-to-injury hypothesis of atherosclerosis currently emphasizes endothelial dysfunction as a result of injury to the endothelial wall.[4] The injury leads to a compensatory response that alters the normal homeostatic properties of the endothelium.[4] Different forms of injury increase the adhesiveness and permeablitiy of the endothelium. The injury also induces the endothelium to have procoagulant instead of anticoagulant properties and to form vasoactive molecules, cytokines, and growth factors.[4] Possible causes of endothelial injury include free radicals caused by: smoking, hypertension, diabetes, hyperhomocystinemia, and elevated low density lipid (LDL).[2,4] Other causes include infections microorganisms such as: cytomegolovirus, *Chlamydia pneumoniae* and *Helicobacter pylori*, and increased C-reactive protein and fibrinogen.[2,4]

Each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process, which if left unchecked will result in a complicated lesion. The lesions occur in large and medium-sized elastic and muscular arteries, which can lead to

ischemia of the heart, brain or extremities, and ultimately infarction.[4] Besides the many probable causes, multiple mechanisms contribute to the atherosclerotic plague formation and its progression. This includes endothelial dysfunction, monocyte adhesion and infiltration, lipid accumulation and oxidation, smooth muscle proliferation, extracellular matrix deposition, and thrombosis[5] (see Figure 1).

Careful history taking and laboratory results can identify patients at risk for atherosclerotic complications such as: myocardiac infarction, stroke or peripheral vascular disease. The standard lipid level screening that includes cholesterol, high-density lipoprotein (HDL), LDL, and trigylcerides, is clinically useful in identifying risk for atherosclerotic events, but half of all myocardial infractions occur in patients with normal plasma lipid levels.[6]

To identify these patients several test have been used in screening to include homocysteine, fibrinogen levels, fibrinolytic capacity, and several different lipoproteins. The clinical value of many of these tests has been limited because of inadequate standardization of assay conditions.[6] Elevated levels of several inflammatory mediators among healthy men and women have proven to be valuable for

predicting future vascular events.[3] Measures of cytokine activity, cellular adhesion, interleukin-6, and intercellular adhesion molecule-1 have been elevated in individuals at increased risk for atherosclerosis.[7] However, the clinical use of these assays needed for assessment are either inappropriate for routine clinical use or the protein of interest has a very short half-life for clinical evaluation.[7] Recently, another inflammatory marker has begun to how promise in predicting atherosclerotic events.

C-Reactive Protein

One of the most promising inflammatory biomarker for the risk of future atherosclerotic events is C-reactive protein (CRP).[3] CRP is produced in response to elevated levels of inter-leukin 6, that occur during the acute phase of inflammation. CRP is a biochemical by-product that can rise following inflammation, infection, and tissue injury.[8] Endothelial tissue can produce low levels of CRP.[8] Although CRP has been shown to be a risk marker for vascular inflammation, evidence has suggested that it can exert proinflammatory effects in endothelial cells.[8,9] The proatherogenic properties of CRP include the activation of endothelial cells to express cell adhesion molecules, chemokines, and endothelin-1.[8] CRP can decrease endothelial nitric oxide synthase expression and activity, and boost

monocyte-endothelial cell adhesion.[9,10] CRP can enhance the uptake of LDL, and it has been shown to be deposited in complex human atherosclerotic plaques.[10]

Ridker et al[11] studied 27,939 women for eight years and found that the CRP level was a stronger predictor of cardiovascular events than the LDL cholesterol level ($p<0.001$).[11] This finding held true after adjustment for age, smoking, the presence or absence of diabetes mellitus, levels of hypertension, and use or nonuse of hormone replacement therapy. [11]

Hormone-replacement therapy affects levels of CRP and LDL cholesterol. Of the 27,939 women in Ridker et al's study, 15,745 were not taking hormone-replacement therapy. This population was divided into increasing quintiles in relation to CRP and LDL cholesterol.[11] The relative risk of new cardiovascular events were computed for quintiles 2-5, with the lowest quintile used as a reference.[11] The results of the relative risks of a first cardiovascular event for women in increasing quintiles of CRP was 1.0, 1.4, 1.6, 2.0 and 2.3, where the relative risk associated with increasing quintiles of LDL cholesterol were 1.0, 0.9, 1.1, 1.3 and 1.5.[11] The strength of CPR over LDL as a predictor of risk for having the following events: coronary heart disease, stroke, and cardiovascular death, can be seen in Figure 2.[11]

Ridker et al's study also showed that increasing CRP levels are associated with increased risk of cardiovascular events at LDL levels below 130, 130-160, and above 160 mg per deciliter (mg/dl).[11] Seventy-seven percent of the first cardiovascular events among the 27,939 women in their study occurred in those with LDL levels below 160 mg/dl, and 46 percent occurred with levels below 130 mg/dl.

Other studies have also suggested that CRP is not only an excellent marker for cardiovascular event, but for other atherosclerotic events as well. Rost et al's[12] study of 591 men and 871 women free of stroke and transient ischemic attack (TIA) demonstrated a strong relationship between CRP and the incidence of first time ischemic stroke or TIA in both sexes.[12] During a 12 to 14 year follow up, 196 ischemic strokes and TIAs had occurred. Men with the highest levels of CRP had twice the risk of ischemic stroke and TIA ($P=0.027$) and the women had almost 3 times the risk ($P=0.0003$).[12] This relationship between the increased incidence of an ischemic event and the increase levels of CRP was shown to persist even after Rost et al adjusted the data for confounders such as: smoking, total/high density lipid cholesterol, systolic blood pressure, and diabetes.[10]

Recently, Ridker et al's[13] prospective cohort study of 14,719 women, suggested an interrelationship between CRP,

metabolic syndrome, and the incidence of cardiovascular events.[13] Metabolic syndrome includes the presence of at least 3 of the following characteristics: abdominal obesity, elevated triglycerides, low HDL cholesterol, high blood pressure, and high fasting glucose.[13] CRP levels were higher among women who had each component of the metabolic syndrome that those who did not ($P<0.0001$). Also, the levels of CRP increased in tandem with the number of expressed characteristics of metabolic syndrome ($P<0.0001$). The women in the study with more than 3 characteristics of metabolic syndrome, and with CRP levels greater than 3 mg/L were at greater risk for having a future cardiovascular events.[13]

C-reactive protein has been shown to be a valuable bio-marker for inflammatory processes, including future risk for cardiovascular events, stroke, TIA, and complications related to metabolic syndrome. How can CRP be used as a primary prevention tool by nurse practitioners?

Clinical applications of CRP

When new prognostic tools are available, clinicians have many questions: How will this help my patients? What is the cost effectiveness? How do I interpret the results? What are the goals of screening?

The standard CRP assay is adequate for evaluation of clinically significant inflammatory processes, but the test

is not precise enough to detect small changes in CRP levels that are linked with cardiovascular risk in what seem to be healthy patients.[8] High-sensitivity CRP (hs-CRP) assays can detect low-grade inflammation within the vascular systems.[8] The hs-CRP assays have been developed and are widely available in most clinical settings throughout the world.[7,10] CRP levels are stable over long periods of time. The levels are not affected by food intake, and have almost no circadian variation, so there is no need for fasting blood samples.[7]

The cost of using hs-CRP to screen for future cardiovascular risk is comparable to a standard cholesterol evaluation.[7] It is suggested that the inexpensive approach of adding hs-CRP to LDL screening may yield an immediate cost savings, by having a negative predictive value and avoiding unnecessary expensive clinical tests.[7]

Interpreting the results of hs-CRP can be seen in Table 1. Patients with hs-CRP levels <1 mg/L are considered at low cardiovascular risk, 1 to 3 mg/L are at moderate risk, and >3mg/L are at high-risk for a future cardiovascular event.[7,10] The hs-CRP levels >10mg/L should be repeated.[7,12] Levels greater than 10 mg/L can be caused by major infections, trauma, or acute hospitalizations.[7]

Even though CRP has been shown to be a stronger predictor of future cardiovascular events than LDL it should not replace LDL in screening patients. The CRP and LDL tests should be used in concert to strengthen risk prediction.[7]

The goal of a cardiovascular screening program is to identify patients at high-risk and to start those individuals on lifestyle modifications as recommended in the Adult Treatment Plan III (ATP III) guidelines. These modifications include: smoking cessation, diet, and exercise.[7] Currently, no definitive evidence shows that lowering CRP will reduce the risk of having a cardiovascular event, but many interventions especially the lifestyle modifications can lead to reduced CRP levels and reduced vascular risk.[7]

Ridker[7] recommends using CRP levels and cholesterol screening in outpatient settings to identify future cardiovascular event risk. The CRP level can be used to maximize the ATP III guideline interventions for the various lipid levels. If a patient's LDL is greater than 160 mg/dL, than an elevated CRP level would reinforce the need to aggressively start pharmacological therapy or to enhance education allowing for better patient adherence to that therapy.[7] With levels between 130 and 160 mg/dL, the nurse practitioner can reinforce education to increase the

patient's adherence to lifestyle modifications. One group of patients that is often missed in clinical practice is individuals with a LDL level below 130 mg/dL, concurrent with CRP levels greater than 3 mg/L. This group will have risk levels as high as other patients with more obvious hyperlipidemia.[7] It is again important to advise the patient to carefully follow the lifestyle modifications and have the patient follow-up to ensure the interventions are effective.

Conclusion

Atherosclerosis is a costly inflammatory disease for which CRP is an excellent biomarker. CRP has been shown to be a better predictor for future cardiovascular events than LDL cholesterol and thus a valuable tool for the primary prevention of atherosclerotic events. When used in concert with LDL, CRP can offer the nurse practitioner an additional avenue to reinforce the need for more aggressive pharmacological therapy and education, saving lives and costly hospitalizations.

References

1. American Heart Association: 2003 heart disease and stroke statistical update. <http://www.americaheart.org> [21 January 2003].

2.Brashers V.: Alterations of cardiovascular function. In: Como D., Dennison B. eds. Pathophysiology: the biologic basis for disease in adults & children. 4th edition. St. Louis MO.: Mosby, 2002;980-1047.

3. Libby P, Ridker PM, Maseri A: Inflammation and atherosclerosis. Circulation 2002;105:1135-1143.

4. Ross R.: Mechanism of disease: artherosclerosis-an inflammatory disease. N Engl J Med 1999;340(2):115-126.

5. Schoen FJ, Cotran RS: Blood vessels. In: Cotran RS, Kumar V, Collins T. eds. Robbins pathologic basis of disease. 6th edition. Philadelphia, PA.:W.B. Saunders, 1999;493-541.

6. Ridker PM, Hennekens CH, Buring JE, et al: C-reactive protein and other markers of inflammation in prediction of cardiovascular disease in women. N Engl J Med 2000;342(12):836-843.

7. Ridker PM: Clinical application of c-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107(3):363-369.

8. Futterman LG, Lemberg L: High-sensitivity c-reactive protein is the most effective prognostic measurement of acute coronary events. Am J Crit Care 2002;11(5):482-486.

9. Sridevi D, Xu DY, Jialal I: C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells-implications for the metabolic syndrome and atherothrombosis. Circulation 2003;107:398-404.

10. Yeh ETH, Willerson JT: Coming of age of c-reactive protein; using inflammation markers in cardiology. Circulation 2003;107:370-372.

11. Ridker PM, Nader R, Lynda R, et al.: Comparison of c-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347(20):1557-1565.

12. Rost NS, Wolf PA, Kase CS, et al.: Plasma concentration of c-reactive protein and risk of ischemic stroke and transient ischemic attack. Stroke 2001;32:2575-2579.

13. Ridker PM, Buring JE, Cook NR, et al: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. An 8-year follow-up of 14,719 initially healthy American women. Circulation 2003;107:391-397.

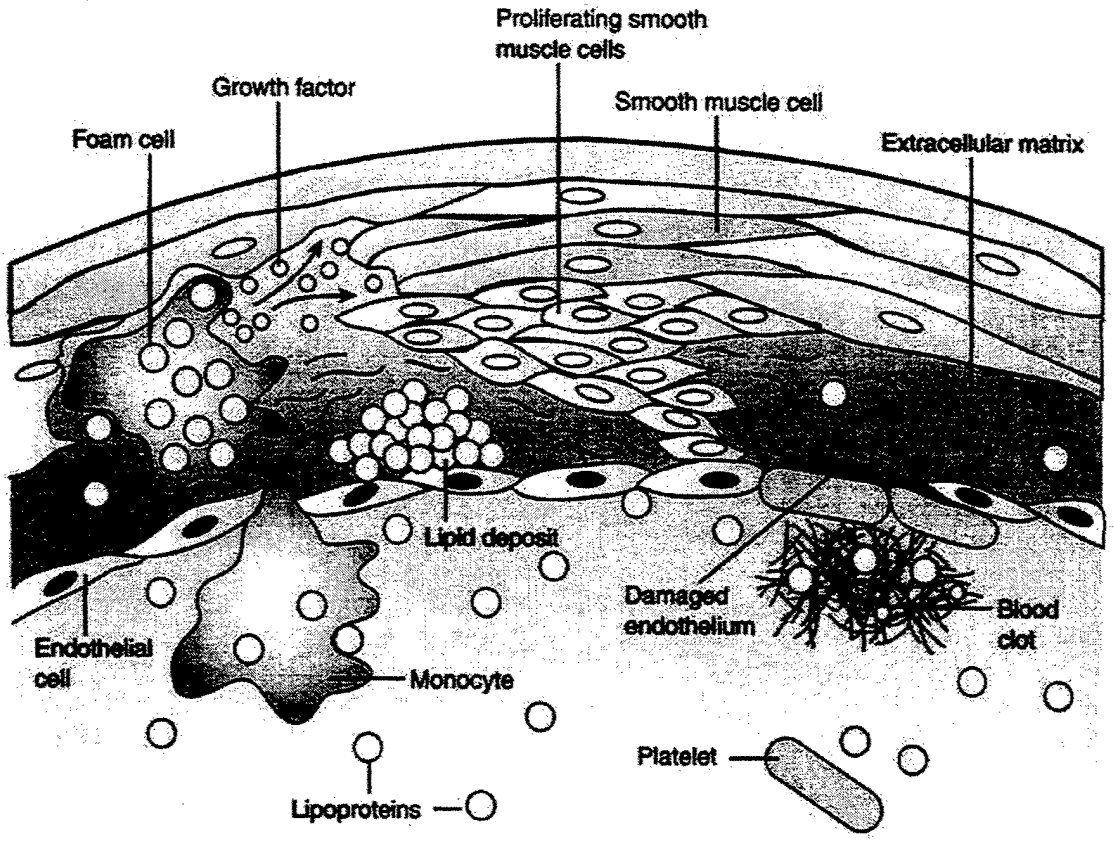

Figure 1 Role of excess lipoprotein and monocyte in the pathogenesis of atherosclerosis. Elevated levels of cholesterol-carrying lipoproteins cause monocytes to attach to and move through cell-to-cell attachments in the endothelium. Monocytes that consume excess lipoproteins become foam cells, which release growth factors that encourage proliferation of smooth muscle cells and extracellular matrix, leading to atherosclerotic plaque formation, endothelial injury, and blood clot formation.

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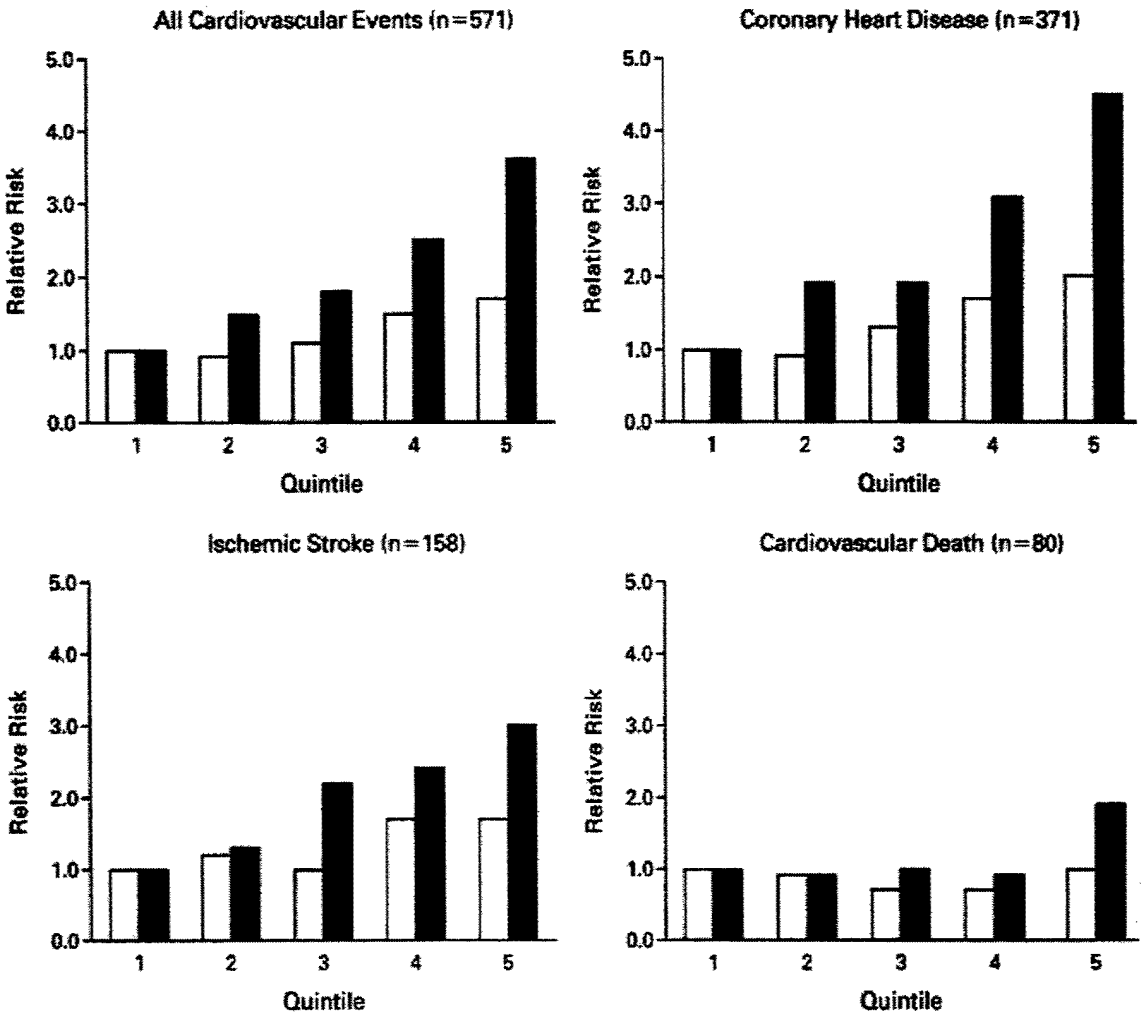

Figure 2 Age-Adjusted Relative Risk of Future Cardiovascular Events, According to Base-Line C-Reactive Protein Levels (Solid Bars) and LDL Cholesterol Levels (Open Bars).
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Table 1
Interpretation of CRP levels

CRP level	**Cardiovascular risk**
<1 mg/L	Low risk
1 mg/L-3 mg/L	Moderate risk
>3mg/L	High risk
≥10 mg/L	Repeat when patient is stable*

*Levels greater than 10 mg/L can be caused by major infections, trauma, or acute hospitalizations